B3

14) when R^5 is substituted phenyl and L is 1,2-ethynyl, then at least one of J^2, J^3, J^4, J^5, and J^6 is not H or null.

B4

30. The compounds of claim 2 wherein R^5 is substituted phenyl; L is furan-2,5-diyl; J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of $-OR^3$, $-SO_2NHR^4$, -CN, –H, halo, $-NR^4{}_2$, $-(CH_2)_2$aryl, $-(CH_2)$NHaryl, and $-NO_2$; at least one Y group is -O-.

REMARKS

In accordance with 37 C.F.R. § 1.121, a marked up copy of the presently amended specification paragraphs and claims is appended hereto. Additions are noted by underlining. Deletions are noted by bracketing. Furthermore, to ensure that Applicants' pending claims match those of the Patent Office, a clean copy of the entire set of pending claims is also appended hereto. No new matter has been added as a result of these amendments.

Claims 1-36 are pending in this application. Claim 7 has been withdrawn from consideration by the Examiner. Claims 1 and 30 have been amended. All of the remaining pending claims stand rejected. The Examiner has indicated that all of the Claims 3-6, 10, 13, 16, 18, 21-28, 30-33, and 35would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, first and second paragraphs, and to include all of the limitations of the base claim and any intervening claims.

The Restriction Requirement

The Examiner has required restriction to one of the following Groups:

I. Claim 30, drawn to phenyl compounds, compounds of formula I(b) with X^3-X^5 = carbon, classified in class 562, subclass 8, among others.

II. Claims none, drawn to pyridine compounds, compounds of formula I(b) with one of X^3-X^5 = nitrogen, classified in class 546, subclass 22, among others.

III. Claims none, drawn to thiophene compounds, compounds of formula I(a) with either G^2 or G^3 = sulfur, classified in class 549, subclass 6, among others.

IV. Claims none, drawn to furan compounds, compounds of formula I(a) with either G^2 or G^3 = oxygen, classified in class 549, subclass 218, among others.

V. Claims none, drawn to oxazoles and thiazoles, compounds of formula I(a) with either G^2 or G^4 = sulfur or oxygen and G^3 = nitrogen, classified in class 548, subclass 119, among others.

VI. Claims none, drawn to all other heteroaryl compounds, classified in class 544, subclass 232, among others.

The Examiner further states that

Claim 7 links Groups III-VI

Claim 8 links Groups I, II, and VI

Claim 14 links Groups I and II

Claims 1-6, 9-13, 15-29, and 31-36 link all Groups.

The Examiner has withdrawn Claim 7 from consideration, as being drawn to a nonelected invention.

The Examiner has rejected Claims 1-6, 8-29, and 31-36 as being drawn to an improper Markush group as *In re Harnisch*. The Examiner states:

> The claimed compounds, compositions, and methods that employ them present a variable core. Formula (Ia) is drawn to the non-elected inventions. Formula (Ib) contains compounds drawn to non-elected inventions. (Office Action p. 4)

According to MPEP § 809, when there are linking claims, the reply to the restriction requirement need only include a proper election.

> The linking claims must be examined with the invention elected, and should any linking claim be allowed the restriction must be withdrawn. MPEP § 809

The Examiner has admitted that Claims 1-6, 9-13, 15-29, and 31-36 link all groups. Therefore, the Applicants believe that they are entitled to leave the claims as is, even though they may be drawn to non-elected inventions. If the claims are amended, they will no longer be linking claims. The Applicants respectfully request that the Examiner remove the rejection that Claims 1-6, 8-29, and 31-36 are drawn to an improper Markush group.

<u>The Information Disclosure Statement</u>

The Examiner indicates that the Applicants' IDS was entered and filed, but that none of the references are presently with the file. Please contact the undersigned if the Examiner would like a duplicate of the references submitted.

The 35 U.S.C. § 112, Second Paragraph Rejections

Claims 1-6 and 8-36 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Applicants respectfully traverse these rejections.

Claims 1-6, 8-17, 19, 26, 30, and 34-36 stand rejected as indefinite, because the Examiner argues that the term "the cyclic moiety contains a carbonate or thiocarbonate" is indefinite. The Examiner says:

> Does contain mean the functional group forms part of the ring, i.e. a 1,3-dioxane is claimed or is a substituent upon the all carbon ring? If the former, the "alicyclic" is improper because such a ring may not contain any heteroatoms. If the former, the "carbonate or thiocarbonate" refer to a group of compounds, not the univalent radicals required as substituents. (Office Action pp. 4-5)

The specification defines the term "alicyclic" as:

> The term "alicyclic" means compounds which combine the properties of aliphatic and cyclic compounds. Such cyclic compounds include but are not limited to, aromatic, cycloalkyl and bridged cycloalkyl compounds. The cyclic compound includes heterocycles. Cyclohexenylethyl and cyclohexylethyl are suitable alicyclic groups. Such groups may be optionally substituted. p. 5

The specification also defines the term "thiocarbonate" as referring to -O-C(S)-O- either in a chain or in a cyclic group. (p. 9)

The specification is clear that the term "alicyclic" can include heterocycles. In addition, the definition of "thiocarbonate" makes it clear that the group must be part of a chain or a ring. Therefore, thiocarbonate can not refer to a substituent on the ring. In light of this, the Applicants believe that one of ordinary skill in the art would understand that the "carbonate or thiocarbonate" is part of the ring. The Applicants respectfully submit that Claims 1-6, 8-17, 19, 26, 30, and 34-36 are definite and request withdrawal of the rejection.

Claims 1-6 and 8-36 stand rejected as indefinite, because the Examiner contends that the phrase "prodrug" is indefinite. The Examiner states that:

Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. (Office Action p. 5)

The Applicants note that the specification at pp. 10-11 defines the term "prodrug" as

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the "drug" substance (a biologically active compound) in one or more steps involving spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), or both. Standard prodrugs are formed using groups attached to functionality, *e.g.* HO-, HS-, HOOC-, R_2N-, associated with the FBPase inhibitor, that cleave *in vivo*. Prodrugs for these groups are well known in the art and are often used to enhance oral bioavailability or other properties beneficial to the formulation, delivery, or activity of the drug. Standard prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. Standard prodrugs of phosphonic acids are also included and may be represented by R^1 in formula I. The groups illustrated are exemplary, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of formula I fall within the scope of the present invention. Prodrugs must undergo some form of a chemical transformation to produce the compound that is biologically active. In some cases, the prodrug is biologically active usually less than the drug itself, and serves to improve efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, etc. pp. 10-11

First, the Applicants note that "prodrugs" are not outside what is claimed. For instance, Claim 1 says "and pharmaceutically acceptable prodrugs and salts thereof."

The Applicants have provided guidance as to what is meant by the term "prodrug." Indeed, the specification at pp. 10-11 points to examples of compounds that are acceptable prodrugs. In addition, the specification gives examples for the preparation of prodrugs of this invention. (*See* Examples 17 and 18, pp. 130-131). Furthermore, prodrug technology is well understood in the art. A person of ordinary skill in the art would have no trouble understanding what is meant by the term "prodrug" as used in the claims of this invention.

The Examiner also objects to the use of a functional definition. As stated in MPEP § 2173.05(g), there is nothing inherently wrong with defining some part of an invention through functional terms. In fact the use of functional language has explicitly been approved by the Court of Appeals.

For instance, *In re Barr*, the U.S. Court of Customs and Patent Appeals approved the use of functional language in defining the term "incapable of forming a dye with said oxidized developing agent." *See In re Barr*, 170 U.S.P.Q. 330, 337 (C.C.P.A. 1971). The Court went on to say that:

> In summary, we hold that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in "functional" terms, and that those "functional" terms may be "negative." The real issue in any such case is not whether the recital is "functional" or "negative," but whether the recital sets definite boundaries on the patent protection sought - that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112. *Id.*

Furthermore, a "limited use of terms of effect or result, which accurately define the essential qualities of a product to one skilled in the art, may in some instances be permissible and even desirable." *In re Fuetterer*, 118 USPQ 217, 222 (C.C.P.A. 1963)(quoting *General Electric Co. v. Wabash Appliance Corp.*, 37 USPQ 466, 469 (U.S. 1938)).

The present situation is similar to the *In re Fuetterer* case. In that case, the examiner and the Board rejected certain composition claims as indefinite, ambiguous, unduly broad, and functional, in part because the term "inorganic salts" was defined in a functional way. *Id.* at 218-219. The examiner stated that:

> "Inorganic salt" reads on literally thousands of materials, many of which would *not be operative* for applicant's purpose. For example, some salts *could* readily react with other ingredients in the composition while other salts *could* be corrosive or destructive of the rubber. This recitation is functional since it merely describes how the salt functions as the surface of the tire wears away. *Id.* at 220.

First, the Court found that use of functional language was proper. *Id.* at 222. Then the Court went on to say that the claims were not unduly broad. *Id.* at 223. The Court stated:

> in the words of the *second* paragraph of section 112, "applicant regards as his invention" the combination with his other tread ingredients of *any* inorganic salt *capable* of "maintaining the carbohydrate, the protein, or mixture thereof, in colloidal suspension* * *." It is exactly this combination which appellant has particularly pointed out and *distinctly claimed* in compliance with the *second* paragraph of section 112...Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloidal suspending properties. We see nothing in the patent law which requires appellant to discover which of all those salts have such properties and which will function in combination. *Id.*

The Court went on to point out that there was no "undue burden" caused by the functional language of the claims:

> The Patent Office would require him to do research on the "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented and is not claiming colloidal suspending agents but tire stock composed of a combination of rubber and other ingredients. *Id.*

Although not directly on point, since the claim in *Fuetterer* was a combination claim, the C.C.P.A. held that the same reasoning applies to elements in claims for compounds. *See In re Barr*, 170 U.S.P.Q. at 336.

As in *Fuetterer*, it would be an undue burden on the Applicant to list each and every suitable prodrug. The desirability of functional language in these claims is clear.

As stated in *Barr*, the real issue is whether the Applicants have set definite boundaries on the patent protection sought. A person of ordinary skill in the art knows what a prodrug is. A person of ordinary skill in the art would also understand what the boundaries of the invention are, particularly when the claims are viewed in light of the specification. Accordingly, there is nothing wrong with defining the term "prodrug" in a functional manner. Nothing requires that the Applicants list each and every suitable prodrug. Therefore, the Applicants respectfully submit that Claims 1-6, 8-36 are definite and request withdrawal of the rejection.

Claim 30 stands rejected as indefinite, because the Examiner argues that there is no antecedent basis for the limitation "J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of OR^3, SO_2NHR^7, -CN, -H, halo, $-NR^4_2$, $-(CH_2)_2$aryl, $-(CH_2)$NHaryl, and $-NO_2$." The Examiner states that there is no antecedent basis for the limitation in Claim 1 which allows J^2 to be either R^2 or OR^{11} only. (Office Action at p. 6) In claim 1, it states that:

> J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of **-H**, **$-NR^4_2$**, $-CONR^4_2$, $-CO_2R^3$, **halo**, **$-S(O)_2NR^4_2$**, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, **alkylaryl**, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, **-alkylene-NR^4_2**, -alkylene-CN, **-CN**, $-C(S)NR^4_2$, **$-OR^2$**, $-SR^2$, $-N_3$, **$-NO_2$**, $-NHC(S)NR^4_2$, and $-NR^{18}COR^2$

The bolded groups above provide the antecedent basis. There was one typographical error in Claim 30, as SO_2NHR^7 should be SO_2NHR^4. With that change, all of the groups in Claim 30 have a proper antecedent basis. The Applicants respectfully submit that Claim 30 is definite and request withdrawal of the rejection.

Claim 34 stands rejected as indefinite, because the Examiner believes that the term "a fructose-1,6-bisphosphate dependent disease" is indefinite. The Examiner contends that it is unclear what diseases and treatments are encompassed by the invention. The Examiner goes on to say:

> A claim is indefinite where it merely recites a use without any active, positive steps delimiting how to practice this use. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out [sic] such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claim is indefinite. (Office Action p. 6)

According to MPEP § 2173.02, the definiteness of claim language must not be analyzed in a vacuum, but in light of:

> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The Applicants note that the term used in the claim is "a fructose-1,6-bisphosphatase dependent disease." The term fructose bisphosphatase is defined in *Stedman's Medical Dictionary*. *Harrison's Principles of Internal Medicine* and *Schiff's Diseases of the Liver* define the term fructose-1,6-diphosphatase deficiency. Copies of these are enclosed for the Examiner's convenience. Given that the term "a fructose-1,6-bisphosphatase dependent disease" is a well known term in the art, a person of ordinary skill in the art would understand what diseases are encompassed by this claim. Applicants believe that a person of ordinary skill in the art could identify a person suffering from a fructose-1,6-bisphosphatase dependent disease. Therefore, the Applicants respectfully submit that Claim 34 is definite and request removal of the rejection.

Claim 36 stands rejected as indefinite, because the Examiner contends that the term "glycogen storage diseases" is indefinite. The Examiner contends that the phrase is not found in *Stedman's*

Medical Dictionary. The Examiner also wants to know if the term "excess glycogen storage diseases" mentioned at p. 4 of the specification is a distinct disease from what is claimed.

First, the Applicants wish to thank the Examiner for pointing out that there is a typographical error on p. 4 of the specification. Applicants meant to use the term "glycogen storage disease" as used in the claim. The Applicants have amended the specification accordingly.

The Applicants note that the term "glycogen storage disease" can be found in *Stedman's Medical Dictionary* as a synonym for glycogenosis. In addition, it can be found in other common texts including *Harrison's Principles of Internal Medicine* and *Schiff's Diseases of the Liver*. The Applicants also note that *Schiff's Diseases of the Liver* at p. 1430 describes various glycogen storage diseases and their synonyms. Copies of these definitions are included for the Examiner's convenience. Given that the term "glycogen storage disease" is a well known term in the art, a person of ordinary skill in the art would understand its meaning, particularly when read in light of the specification. Therefore, the Applicants respectfully submit that Claim 36 is definite and request removal of the rejection.

The 35 U.S.C. § 112, First Paragraph Rejections

Claims 1-6 and 8-36 are rejected under 35 U.S.C. § 112, first paragraph as not enabled. The Applicants respectfully traverse these rejections.

Claims 1-6 and 8-36 stand rejected as not enabled, because the Examiner believes that determining if a substance is a "prodrug" will require undue experimentation. The Examiner argues:

> For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, the second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting passes the threshold of undue experimentation. (Office Action p. 7)

As noted above, the term "prodrug" is defined in the specification as:

> The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the "drug" substance (a biologically active compound) in one or more steps involving spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), or both. Standard prodrugs are formed using groups attached to functionality, *e.g.* HO-, HS-, HOOC-, R_2N-, associated with the FBPase inhibitor, that cleave *in vivo*. Prodrugs for these groups are well known in the art and are often used to enhance oral bioavailability or other properties beneficial to the formulation, delivery, or activity of the drug. Standard prodrugs

> include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. Standard prodrugs of phosphonic acids are also included and may be represented by R^1 in formula I. The groups illustrated are exemplary, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of formula I fall within the scope of the present invention. Prodrugs must undergo some form of a chemical transformation to produce the compound that is biologically active. In some cases, the prodrug is biologically active usually less than the drug itself, and serves to improve efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, etc. pp. 10-11

First, the Applicants note that according to the above definition and what is known in the art, "in some cases, the prodrug is biologically active usually less than the drug itself, and serves to improve efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, etc." Therefore, the first test suggested by the Examiner is not a requirement per se for prodrugs. However, determining whether a compound meets any of the three criteria set out by the Examiner requires only routine testing.

A person of ordinary skill in the art understands how to make a prodrug and determine if a compound is suitable as a prodrug. A myriad of references describe the routine preparation of prodrugs. A small sample is enclosed for the Examiner's perusal and convenience: *Comprehensive Medicinal Chemistry*, v.5, 122-133 (1990); Sanchez et al., *Quinoline Antibacterial Agents: Synthesis and Structure-Activity Relationships of a Series of Amino Acid Prodrugs of Racemic and Chiral 7-(3-Amino-1-pyrrolidinyl)quinolines. Highly Soluble Quinoline Prodrugs with In Vivo Pseudomonas Activity*, J.Med. Chem. 35:1764-1773 (1992); Serafinowksa et al., *Synthesis and In Vivo Evaluation of Prodrugs of 9-[2-(Phosphonomethoxy)ethoxy]adenine*, J. Med. Chem. 38:1372-1379 (1995); Bundgaard and Nielsen, *Esters of N,N-Disubstituted 2-Hydroxyacetamides of a Novel Highly Bioavailable Prodrug Type for Carboxylic Acid Agents*, J. Med. Chem. 30:451-454 (1987); Chong et al., *Peptidomimetic HIV Protease Inhibitors: Phosphate Prodrugs with Improved Biological Activities*, J. Med. Chem. 36:2575-2577 (1993). Indeed, prodrugs have been long known, the authors of the article in *Comprehensive Chemistry* note that aspirin and hexamine are prodrugs that were developed in the late 19th century. *Comprehensive Chemistry* at p. 124. Since prodrug technology is well-understood in the art, no undue experimentation is required in order that a person of ordinary skill in the art can make and use the invention.

In addition, the specification gives examples for the preparation of prodrugs of this invention. (*See* Examples 17 and 18, pp. 130-131). According to MPEP § 2164.01(b), "As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." The Applicants submit that they have thus satisfied the enablement requirement. Therefore, the Applicants respectfully request withdrawal of the rejection that Claims 1-6 and 8-36 are not enabled.

Claims 34 and 36 stand rejected as not enabled, because the Examiner contends that while the specification is enabling for treatment of diabetes, it is not enabling for treatment of "a fructose-1,6-biphosphatase dependent disease" or "glycogen storage diseases" generally. The Examiner states:

> Applicants have not demonstrated nor have they alleged there is any correlation between the *in vitro* assay, whose results are described in Table 3, page 133, and clinical efficacy against any specific disease. Case law is clear on this point. In an unpredictable art, such as diabeteis [sic] pharmacology, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy. (Office Action pp. 7-8).

According to MPEP § 2164.02, the correlation between *in vitro* and *in vivo* is dependant upon the state of the prior art. "In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." MPEP § 2164.02 The examples described in the application are all recognized models for testing the effectiveness of drugs in treating diabetes and related diseases. For instance, Example A (pp. 132-33) shows that the compounds of this invention are useful in inhibiting human and rat liver FBPase. Diabetes is an FBPase dependent disease. In fact, medical dictionaries correlate diabetes and related diseases to FBPase. Therefore, there is a reasonable correlation between the models and a fructose-1,6-bisphosphatase dependent disease or a glycogen storage disease.

In addition, there are numerous references that describe the correlation of *in vitro* and *in vivo* testing in regard to diabetic individuals. Included for the Examiner's convenience are two such abstracts from Pub.Med. (a Federal Government database): Muller et al., *Action of Metformin on Erytrhocyte Membrane Fluidity In Vitro and In Vivo*, Eur. J. Pharmacol. 15:337(1):103-10 (1997); Chen et al., *Reactive Oxygen Species Enhances Endothelin-1 Production of Diabetic Rat Glomeruli in Vitro and In*

Vivo, J. Clin. Med. 135(4):309-15 (2000). In view of the above, Applicants respectfully request removal of the rejection that Claims 34 and 36 are not enabled.

The 35 U.S.C. § 102 Rejection

Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,640,701 ("the '701 patent"). The Examiner contends that two of the compounds taught by the '701 patent fit formula I compounds of the above claims.

Since the Applicants have amended the claims to exclude these two compounds, they believe that this rejection is now moot. Therefore, Applicants respectfully request the removal of this rejection.

Conclusion

In view of the above remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

Respectfully Submitted,

Date: 8/13/02

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Marked Up Version of the Specification

At p. 4, lines 1-4:

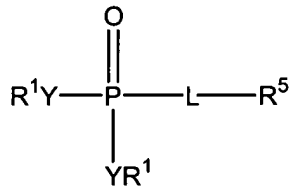
The compounds are also useful in treating or preventing [excess] glycogen storage diseases and diseases such as cardiovascular diseases including atherosclerosis, myocardial ischemic injury, and diseases such as metabolic disorders such as hypercholesterolemia, hyperlipidemia which are exacerbated by hyperinsulinema and hyperglycemia.

p. 10, line 24 – p. 11, line 6, to read as follows:

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the "drug" substance (a biologically active compound) in <u>one</u> or more steps involving spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), or both. Standard prodrugs are formed using groups attached to functionality, *e.g.* HO-, HS-, HOOC-, R_2N-, associated with the FBPase inhibitor, that cleave *in vivo*. Prodrugs for these groups are well known in the art and are often used to enhance oral bioavailability or other properties beneficial to the formulation, delivery, or activity of the drug. Standard prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. Standard prodrugs of phosphonic acids are also included and may be represented by R^1 in formula I. The groups illustrated are exemplary, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of formula I fall within the scope of the present invention. Prodrugs must undergo some form of a chemical transformation to produce the compound that is biologically active. In some cases, the prodrug is biologically active usually less than the drug itself, and serves to improve efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, etc.

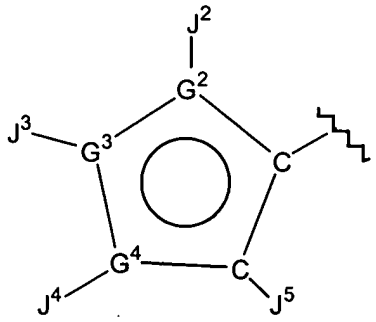
Marked Up Version of the Claims

1. (Amended) A compound of formula (I):

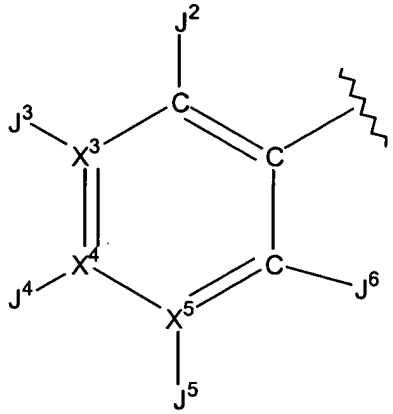


(I)

wherein R^5 is selected from the group consisting of:



and



I (a) **I (b)**

wherein:

G^2 is selected from the group consisting of C, O, and S;

G^3 and G^4 are independently selected from the group consisting of C, N, O, and S;

wherein a) not more than one of G^2, G^3, and G^4 may be O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2, G^3, and G^4 is C; and d) G^2, G^3, and G^4 are not all C;

X^3, X^4, and X^5 are independently selected from the group consisting of C and N, wherein no more than two of X^3, X^4, and X^5 may be N;

J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylenearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, -alkylene-NR^4_2, -alkylene-CN, -CN, $-C(S)NR^4_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4_2$, and $-NR^{18}COR^2$;

L is selected from the group consisting of:

i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, -pyrimidinyl-, –pyrazinyl-, and -alkynyl-, all of which may be optionally substituted; and

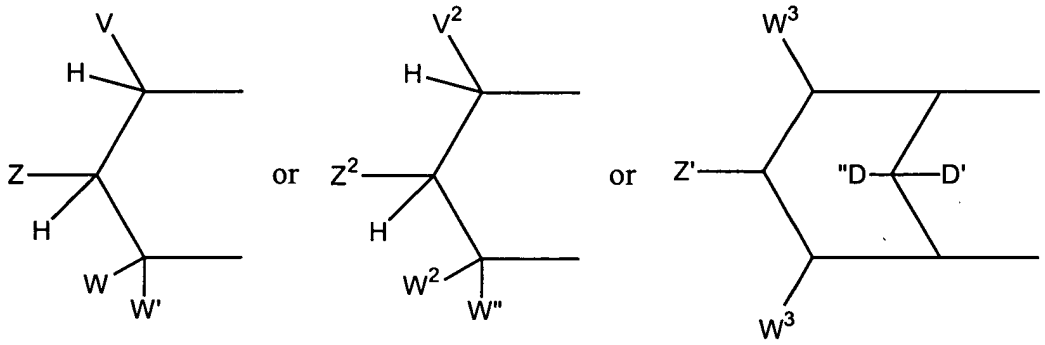
ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –alkylenecarbonylamino-, -alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, -alkyleneoxy-, and –alkyleneoxyalkylene-, all of which may be optionally substituted;

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted arylalkylene-, -$C(R^2)_2OC(O)NR^2_2$, -NR^2-C(O)-R^3, -$C(R^2)_2$-$OC(O)R^3$, -$C(R^2)_2$-O-$C(O)OR^3$, -$C(R^2)_2OC(O)SR^3$, -alkylene-S-$C(O)R^3$, -alkylene-S-S-alkylenehydroxy, and -alkylene-S-S-S-alkylenehydroxy,

when one Y is –NR^6-, and R^1 attached to it is –$(CR^{12}R^{13})_n$-C(O)-R^{14}, then the other YR^1 is selected from the group consisting of –$NR^{15}R^{16}$, -OR^7, and NR^6-$(CR^{12}R^{13})_n$-C(O)-R^{14};

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkylene-S-S-alkylene- to form a cyclic group, or together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of –CHR^2OH , -$CHR^2OC(O)R^3$, -$CHR^2OC(S)R^3$, -$CHR^2OC(S)OR^3$, -$CHR^2OC(O)SR^3$, -$CHR^2OCO_2R^3$, -OR^2 , -SR^2, -CHR^2N_3, -CH_2aryl, -CH(aryl)OH, -$CH(CH=CR^2_2)OH$, -$CH(C\equiv CR^2)OH$, -R^2 , -NR^2_2, -$OCOR^3$, -OCO_2R^3, -$SCOR^3$, -SCO_2R^3, -$NHCOR^2$, -$NHCO_2R^3$, -CH_2NHaryl, -$(CH_2)_p$-OR^{19}, and -$(CH_2)_p$-SR^{19}; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W′ are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-SR^2$, $-CH_2NHaryl$, $-CH_2aryl$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D" is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W" are not all –H ; and

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group consisting of O, N, and S;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, aryl, aralkyl, alkyloxycarbonyloxyalkyl, and lower acyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

R^7 is lower R^3;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$; and

each R^{12} and R^{13} is independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2OR^{20}$;

R^{15} is selected from the group consisting of –H, lower aralkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{18} is selected from the group consisting of –H and lower R^3;

R^{19} is selected from the group consisting of –H, and lower acyl;

R^{20} is selected from the group consisting of –H, lower R^3, and –C(O)-(lower R^3);

n is an integer from 1 to 3;

with the provisos that:

1) when X^3, X^4, or X^5 is N, then the respective J^3, J^4, or J^5 is null;

2) when L is substituted furanyl, then at least one of J^2, J^3, J^4, and J^5 is not –H or null;

3) when L is not substituted furanyl, then at least two of J^2, J^3, J^4, and J^5 on formula I(a) or J^2, J^3, J^4, J^5, and J^6 on formula I(b) are not –H or null;

4) when G^2, G^3, or G^4 is O or S, then the respective J^2, J^3, or J^4 is null;

5) when G^3 or G^4 is N, then the respective J^3 or J^4 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

6) if both Y groups are $-NR^6-$, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n-C(O)-R^{14}$;

7) when L is –alkylenecarbonylamino- or -alkyleneaminocarbonyl-, then X^3, X^4, and X^5 are not all C;

8) when L is –alkeneoxyalkylene-, and X^3, X^4, and X^5 are all C, then neither J^3 nor J^5 can be substituted with an acylated amine;

9) when R^5 is substituted phenyl, then J^3, J^4, and J^5 is not purinyl, purinylalkylene, deaza-purinyl, or deazapurinylalkylene;

10) R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^6-C(R^{12}R^{13})_n-C(O)-R^{14}$;

11) when R^5 is substituted phenyl and L is 1,2-ethynyl, then J^3 or J^5 is not a heterocyclic group;

12) when L is 1,2-ethynyl, then X^3 or X^5 cannot be N;

and pharmaceutically acceptable prodrugs and salts thereof[.];

13) when R^5 is substituted phenyl and L is –alkyleneoxycarbonyl-, then J^3 or J^5 is not O-aryl;

14) when R^5 is substituted phenyl and L is 1,2-ethynyl, then at least one of J^2, J^3, J^4, J^5, and J^6 is not H or null.

30. (Amended) The compounds of claim 2 wherein R^5 is substituted phenyl; L is furan-2,5-diyl; J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of $-OR^3$, $-SO_2NHR[^7]^4$, -CN, –H, halo, $-NR^4_2$, $-(CH_2)_2$aryl, $-(CH_2)$NHaryl, and $-NO_2$; at least one Y group is -O-.